Estimating the incidence of atrial fibrillation in single-chamber implantable cardioverter defibrillator patients

Zweibel, Steven ; Cronin, Edmond M ; Schloss, Edward J ; Auricchio, Angelo ; Kurita, Takashi ; Sterns, Laurence D ; Gerritse, Bart ; Lexcen, Daniel R ; Cheng, Alan

Abstract: BACKGROUND Atrial arrhythmias are associated with major adverse cardiovascular events. Recent reports among implantable cardioverter defibrillator (ICD) patients have demonstrated a high prevalence of atrial fibrillation (AF), predominantly in dual-chamber recipients. AF incidence among patients with single-chamber systems (approximately 50% of all ICDs) is currently unknown. The objective was to estimate the prevalence of new-onset AF among single-chamber ICD patients by observing the rates of new atrial tachycardia (AT)/AF among a propensity scoring matched cohort of dual-chamber ICD patients from the PainFree SST study, to better inform screening initiatives. METHODS Among 2,770 patients enrolled, 1,862 single-chamber, dual-chamber, and cardiac resynchronization therapy (CRT) subjects with no prior history of atrial tachyarrhythmias were included. Daily AT/AF burden was estimated using a propensity score weighted model against data from dual-chamber ICDs. RESULTS Over 22 ± 9 months of follow-up, the estimated incidence of AT/AF - lasting at least 6 minutes, 6 hours and 24 hours per day - in the single-chamber cohort was 22.0%, 9.8% and 6.3%, whereas among dual-chamber patients, the prevalence was 26.6%, 13.1%, and 7.1%, respectively. Initiation of oral anticoagulation (OAC) was estimated to occur in 9.8% of the propensity matched single-chamber cohort, which was higher than the actual observed rate of 6.0%. Stroke and transient ischemic attack (TIA) occurred at low rates in all device subgroups. CONCLUSIONS Atrial arrhythmias occur frequently, and significant underutilization of anticoagulation is suggested in single-chamber ICD recipients. Routine screening for AF should be considered among single-chamber ICD recipients.

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Estimating the Incidence of Atrial Fibrillation in Single-Chamber Implantable Cardioverter Defibrillator Patients

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ABSTRACT

Background

Atrial arrhythmias are associated with major adverse cardiovascular events. Recent reports among implantable cardioverter defibrillator (ICD) patients have demonstrated a high prevalence of atrial fibrillation (AF), predominantly in dual-chamber recipients. AF incidence among patients with single-chamber systems (approximately 50% of all ICDs) is currently unknown. The objective was to estimate the prevalence of new-onset AF among single-chamber ICD patients by observing the rates of new atrial tachycardia (AT)/AF among a propensity scoring matched cohort of dual-chamber ICD patients from the PainFree SST study, to better inform screening initiatives.

Methods

Among 2,770 patients enrolled, 1,862 single-chamber, dual-chamber, and cardiac resynchronization therapy (CRT) subjects with no prior history of atrial tachyarrhythmias were included. Daily AT/AF burden was estimated using a propensity score weighted model against data from dual-chamber ICDs.

Results

Over 22 ± 9 months of follow-up, the estimated incidence of AT/AF - lasting at least 6 minutes, 6 hours and 24 hours per day - in the single-chamber cohort was 22.0%, 9.8% and 6.3%, whereas among dual-chamber patients, the prevalence was 26.6%, 13.1%, and 7.1%, respectively. Initiation of oral anticoagulation (OAC) was estimated to occur in 9.8% of the propensity matched

single-chamber cohort, which was higher than the actual observed rate of 6.0%. Stroke and transient ischemic attack (TIA) occurred at low rates in all device subgroups.

Conclusions

Atrial arrhythmias occur frequently, and significant underutilization of anticoagulation is suggested in single-chamber ICD recipients. Routine screening for AF should be considered among single-chamber ICD recipients.

KEYWORDS

Cardiac implantable electronic device

Implantable cardioverter defibrillator

Cardiac resynchronization therapy

Atrial fibrillation

Atrial tachyarrhythmia

Stroke

INTRODUCTION

Co-morbidities that predispose to the development of systolic heart failure and sudden cardiac death often are also those that increase the risk for the development of atrial fibrillation (AF).[1-3] AF can present asymptomatically and given its strong association with

stroke,[4] recent attention has focused on identifying ways in which to more efficiently and effectively screen for its presence.[5]

While the utility of screening the entire general population is controversial, most agree that identifying high risk populations to screen is justifiable since the prevalence within such groups may result in higher yield. Some experts support the use of opportunistic screening based on age alone[6] but there are other populations that may benefit more including those with heart failure or individuals at increased risk for sudden cardiac death. In order to justify such efforts, an understanding of the true prevalence of AF in these populations is necessary. Individuals with implantable cardioverter defibrillators (ICDs) are one such population. In fact, among patients with dual-chamber ICDs, the incidence of newly detected atrial arrhythmias has been reported to be greater than 20% yearly across two separate investigations.[7, 8] Since there is an increasing percentage of ICD patients undergoing implantation of a single-chamber system,[9] these estimates may not be representative of the larger ICD population. The objective of this analysis was to estimate the incidence of newly detected AT/AF among single-chamber ICD recipients by observing the rates of new AT/AF among a propensity scoring matched cohort of dual-chamber ICD patients from the PainFree SST study.

METHODS

Study design and patients

PainFree SST was a large multicenter clinical trial that aimed to evaluate if SmartShock® technology (SST) device detection algorithms reduce inappropriate ICD shocks. The study design and

primary results have been published previously.[10, 11] The study was performed in compliance with the Declaration of Helsinki.[12] The institutional review board of each participating center approved the study protocol, and all patients provided written informed consent. Among 2,770 patients implanted with a Medtronic Protecta® (Medtronic plc, MN, U.S.) single-chamber, dual-chamber or cardiac resynchronization defibrillator (CRT-D) enrolled in the study, 1,862 subjects with no prior history of atrial arrhythmias (AF, atrial flutter, atrial tachycardia) were included in this analysis.

Device data were downloaded at patient visits and used for this analysis. Newly detected episodes of AT/AF was determined by assessing total daily AT/AF burden (total AF duration/24 hour period) of atrial high rate events greater than 175 beats per minute for the preceding 425 days.[13] Endpoints for analysis of AT/AF incidence were the first day with a total AT/AF burden of 6 minutes, 6 hours, 24 hours, and the first 7 consecutive days with 24 hours of AT/AF. Serious adverse events were collected only for patients enrolled from European sites [11] and were considered an AT/AF related complication if stroke, TIA, thrombosis or AT/AF was reported as a primary or secondary finding.

Since no AT/AF data were collected in single-chamber ICD subjects, the likelihood that a single-chamber patient would develop new onset of AF was estimated from the incidence of AT/AF in dual-chamber patients. A propensity model was used to derive weights for the 649 dual-chamber patients, such that applying the weights would render the cohort comparable at baseline to the 574 single-chamber patients. Incidence of AT/AF in the single-chamber cohort was then estimated by applying the same weights to the AT/AF incidence data of the dual-chamber patients. This will be referred to as “Matched Single-Chamber”.

Statistical analysis

To account for missing data, multiple imputation from the chained equations method was used to create 25 completed baseline data sets with any missing values randomly chosen from the distribution of values that were plausible for the patient accounting for all other baseline characteristics. There were 2 variables with more than 3 missing values: left ventricular ejection fraction (LVEF) in 101 patients (8.3%) and QRS duration in 94 patients (7.7%).

Logistic regression was used to model the probability that a patient received a single-chamber ICD accounting for baseline characteristics (the propensity). All characteristics with a significant baseline difference were included, as well as gender, LVEF, New York Heart Association (NYHA) functional class, coronary artery disease, congestive heart failure, prior ventricular fibrillation (VF), treatment with angiotensin converting enzyme (ACE) inhibitor or angiotensin-II-receptor blocker (ARB), beta-blocker, diuretic, calcium channel blocker, or anti-coagulant.

Analysis of AT/AF incidence used survival analysis methods including weighted and unweighted Kaplan-Meier estimation. Dual-chamber ICD patients have a weight assigned depending on how likely the implantation of a single-chamber device would have been given the patient's baseline characteristics. The weight is calculated as $p / (1 - p)$, where p represents the probability of getting a single-chamber device (propensity). A weight of 1 is assigned to single-chamber patients and used for those analyses that compare single-chamber and weighted dual-chamber patients [Inverse Probability of Treatment Weighting (IPTW)].[14] Results from weighted analysis of dual-chamber patients are presented as "Matched Single-Chamber".

RESULTS

Among the 1,862 patients without a history of atrial tachyarrhythmias [AF, atrial flutter, AT], 639, 649, and 574 patients received a CRT, dual-chamber, and single-chamber ICD system, respectively (**Figure 1**). The mean follow-up time for this cohort was 22 ± 9 months. Patient baseline characteristics are outlined in **Table 1**. While the overall makeup of the population is reflective of the major clinical trials, significant differences existed between the dual-chamber and single-chamber ICD subjects.

Incidence rates of AT/AF among CRT and dual-chamber ICD patients for various degrees of AT/AT burden are displayed in **Figure 2**. Of note, the proportions of CRT or dual-chamber ICD patients who experienced at least one day with more than 6 hours of total AF duration were observed to be 16.3% and 13.1% at 24 months, respectively. The estimated incidence rate of AT/AF burden of at least 6 hours in the matched single-chamber cohort was 9.8%. Incidence of newly detected AT/AF varied strongly by endpoint definition used and by device type (**Table 2**). The largest proportion of subjects with AT/AF burden lasting 7 days was observed in the CRT group with a rate of 8.2%. However, when comparing rates of AT/AF lasting greater than 7 days between dual-chamber ICD and matched single-chamber ICD subjects, the observed and estimated rates were 3.8% and 3.4%, respectively.

Initiation of OAC in subjects without a history of atrial tachyarrhythmias was observed in 7.2% of the dual-chamber ICD subjects. Within the matched single-chamber ICD cohort, the

incidence where new OAC initiation might be warranted was 9.8% whereas the actual observed rate of OAC initiation was 6.0 % (**Figure 3**). Of the total subjects receiving OAC, not all had device-detected AT/AF. Initiation of OAC and newly detected AT/AF (defined as a day with > 6 hours of AT/AF) occurred simultaneously in 3.5% of the dual-chamber ICD cohort and was estimated to occur in 3.4% of the matched single-chamber ICD cohort.

Stroke and transient ischemic attack (TIA) information were collected in the European patients (n = 677). At 24 months, there was a low rate of stroke or TIA in the CRT-D (2.2%) and dual-chamber ICD (2.5%) cohorts. Within the single-chamber ICD cohort, a rate of 0.8% was observed. The low event rate did not permit further analysis according to anticoagulation status.

DISCUSSION

AF is common and recent studies have demonstrated a high incidence over time.[15] Utilizing data collected from the PainFree SST study and modeling with propensity-scored matching, this analysis of ICD patients without a prior history of atrial tachyarrhythmias demonstrate that (1) newly detected AT/AF is common, (2) AT/AF is estimated to occur in 22% of single-chamber ICD patients by two years from the date of implant, and (3) the incidence of newly detected AT/AF is comparable in single- and dual-chamber ICD patients even though it tends to be lower in single-chamber.. Taken together, the results extend our current understanding of AF among patients with devices and call attention to the need to identify ways to properly screen those at increased risk of AT/AF development over time.

In the present analysis, AT/AF burden lasting ≥ 6 minutes was observed in 29.7% of the CRT-D patients, 26.6% of the dual-chamber ICD patients and estimated to occur in 22.0% of propensity score matched single-chamber ICD patients within two years of device implantation. These results are consistent with a prior study[7] that evaluated newly detected AF among pacemaker, ICD, and CRT patients stratified by stroke risk. Our findings expand upon previous investigations by highlighting the differences in newly observed AF observed across different ICD device types.

The accuracy of the modeled rate of AF among single-chamber patients in our analysis is highly dependent on the degree of similarity between the dual- and single-chamber ICD patients. Since the propensity scores matching methodology took into account differences in baseline conditions, the influence of factors like AV block and SND were minimized as much as possible. While prior studies have suggested that atrial pacing may have a small role in reducing AF,[16] the impact of this is likely low in this analysis given that only 12.9% of dual chamber patients had an indication for pacing.

The overall incidence of AT/AF and rapid onset of newly detected AT/AF across all device types have important clinical implications. Without the presence of an atrial lead, the single-chamber population is limited by relying on symptoms or serendipitous detection to diagnose AF, whereas dual-chamber and CRT patients are constantly being monitored. Given the increased risk for stroke associated with device-detected AT/AF events, we observed a large proportion (22.0%) of the single-chamber ICD population that could potentially benefit from continuous AF screening. Currently, single-chamber AF screening can only be done via a Visia AF Single Chamber ICD (Medtronic plc, Minneapolis, MN, USA) which contains R wave to R wave interval variability-based algorithms

capable of detecting AT/AF [17] or a Linox Smart DX ICD lead and DX ICD (Biotronik, Berlin, Germany) which contains a floating atrial dipole to detect atrial signals.[18] These technologies are likely to provide additional supporting evidence of the true AT/AF incidence in single-chamber subjects in the future, but current evidence is lacking. Another interesting observation was that the rate of newly detected AF of more than 6 minutes per day is much higher in the initial months post-implant for all device types. There may be several explanations for this, but the most likely may be that patients receiving devices have underlying AF that was asymptomatic, or subclinical in nature. A sub analysis from the ASSERT trial demonstrated that previously undiagnosed subclinical AF is common in ICD and pacemaker populations.[19] By implanting a device with continuous AF monitoring, it is likely there is an initial spike in AF detection occurring in patients who had undocumented subclinical AF at the time of implant.

The duration of AT/AF that should trigger initiation of anticoagulation in device patients is controversial. Studies have demonstrated that device-detected episodes of AF ranging in duration from 5 minutes to 24 hours are associated with increased risk of stroke, with the clearest evidence for an increased risk for episodes of 24 hours or more. [19] A recent consensus document has recommended initiation of oral anticoagulation in appropriate device patients with > 5.5 hours of daily AF burden[20] while others have suggested shorter and longer AF durations dependent on a patient's underlying risk for stroke. [21] Regardless of the actual cut-off used, our data demonstrate that AT/AF is common and steadily increases over time.

We also analyzed the incidence of new initiation of OAC within the first 24 months and found that there was a gap between the actual use of OAC in the single-chamber ICD subjects (5.8%) versus the expected use of OAC in this group (9.8%). This is likely due to under detection of subclinical AF in the single-chamber ICD patients given the lack of an atrial lead in these devices. It

is possible that detection of AT/AF in the single-chamber ICD population could have resulted in a higher rate of OAC initiation and reduction in thromboembolic events. Unfortunately, thromboembolic events were only collected in a subset of patients and occurred at a very low rate. Hence, no meaningful comparison could be made.

Limitations

Our study has several limitations that should be considered when interpreting the results. In this analysis, device detected AT/AF was used and was not independently adjudicated. Additionally, AT/AF may be under-detected by ICDs due to undersensing or over-detected due to oversensing of other signals. This may lead to systematic over- or underestimation of AT/AF incidence, or more likely, regression to the mean. Hence, we used the AT/AF burden metric rather than the duration of each episode to potentially account for brief periods of undersensing. Second, complete adverse event data, specifically stroke, were collected only in the European subset of patients, limiting statistical power for analysis of these events. Third, we were unable to report the CHADS2 or CHA2DS2-VASc scores as not all the necessary data points were collected at baseline. Finally, the propensity matching successfully balanced observed patient characteristics, but may not have accounted for factors that were not collected in PainFree SST. The overall rate of atrial pacing by dual-chamber devices may have influenced the incidence rate of AT/AF and may serve as a confounding factor.

Conclusions

Atrial arrhythmias are common among single-chamber ICD recipients with 22.0%, 9.8% and 6.3% developing an episode of at least 6 minutes/day, 6 hours/day and 24 hours/day, respectively, over 24 months. The observed rate of new anticoagulation prescription was less in the single-chamber

ICD population than the predicted AT/AF incidence, suggesting a role for algorithms which can detect AT/AF in single-chamber ICDs to increase AT/AF detection and appropriate OAC initiation.

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FIGURE LEGENDS

Figure 1. Patient Flow Diagram

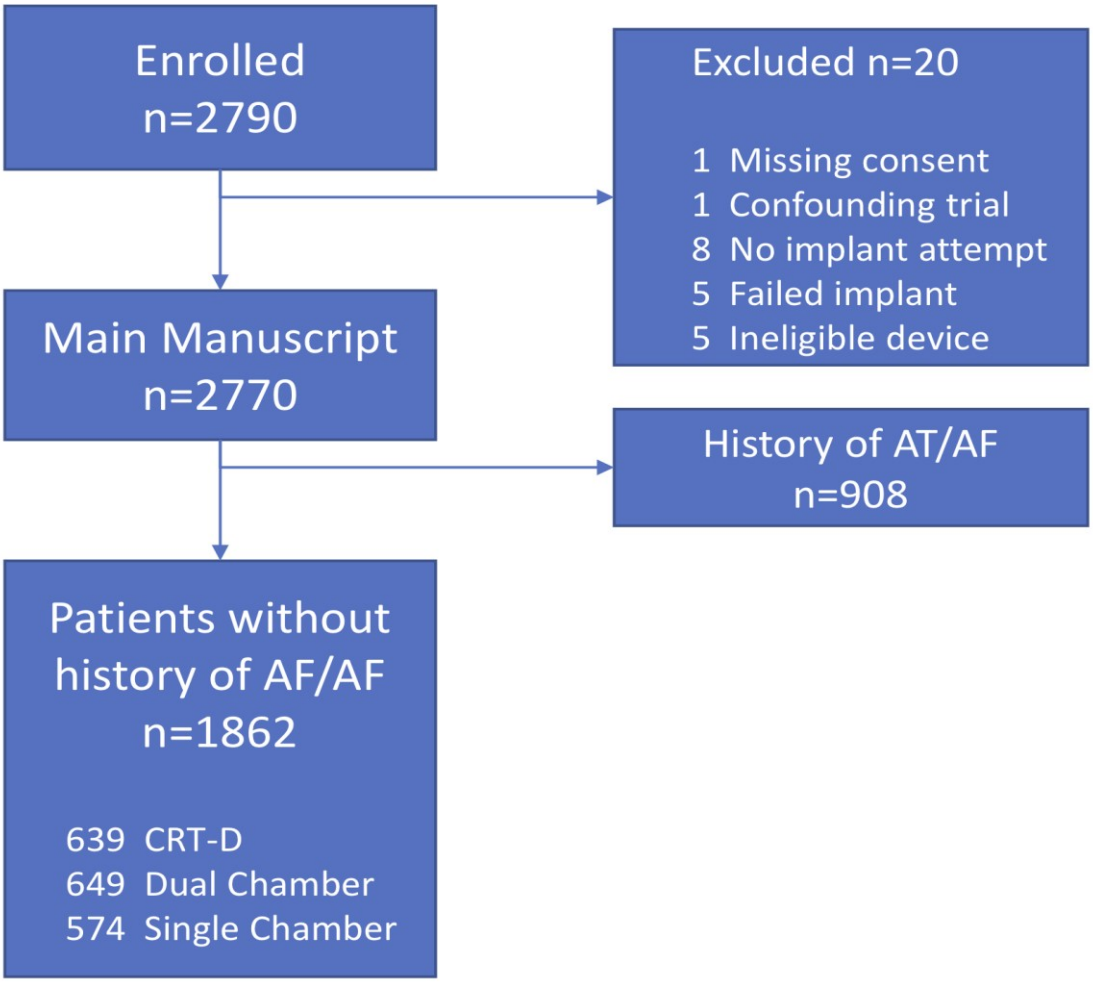


Figure 2. Time to First Occurrence of Different Daily AT/AF Burdens among CRT, Dual-Chamber ICD, and Matched Single-Chamber ICD Cohorts without a Prior History of Atrial Tachyarrhythmias.

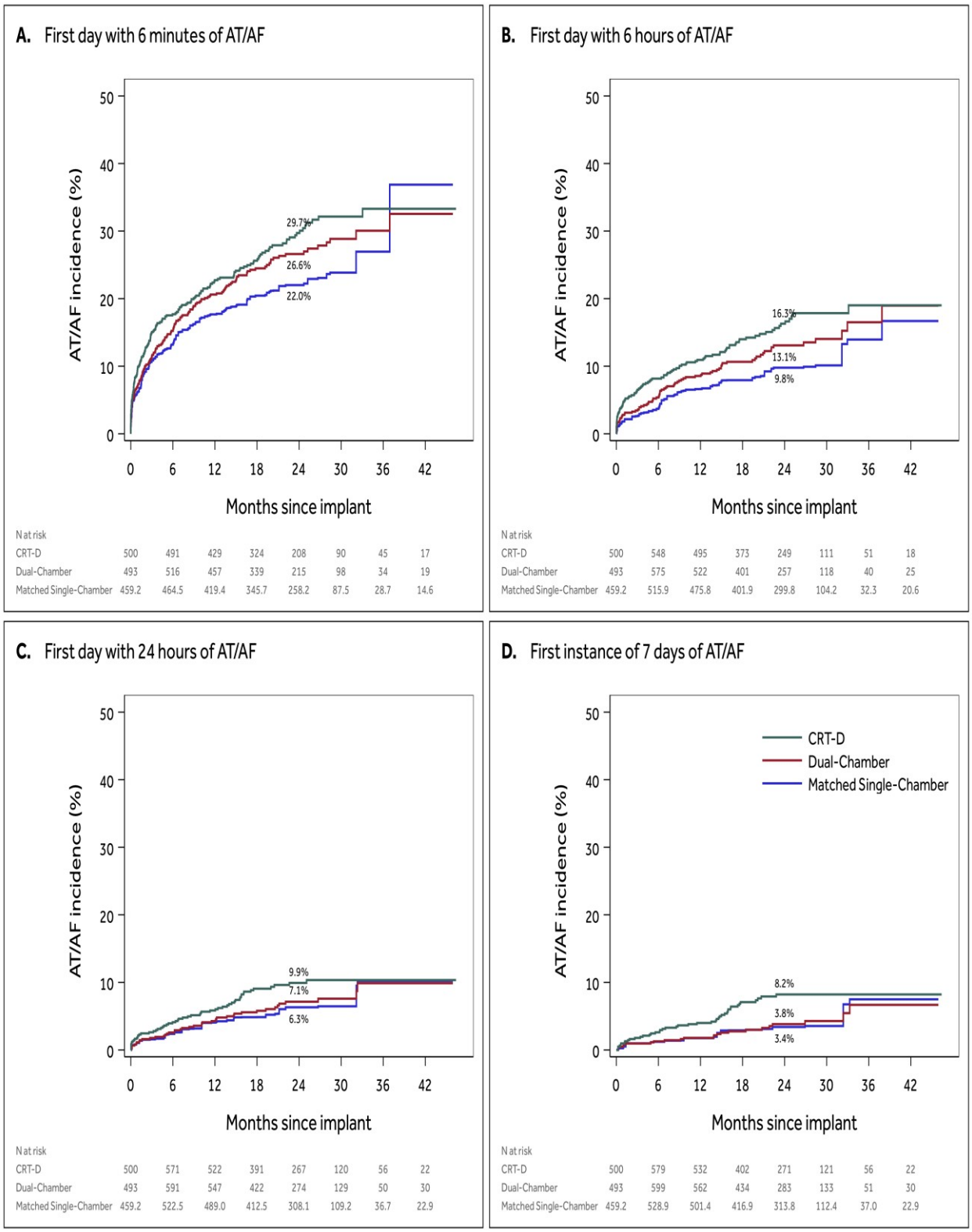
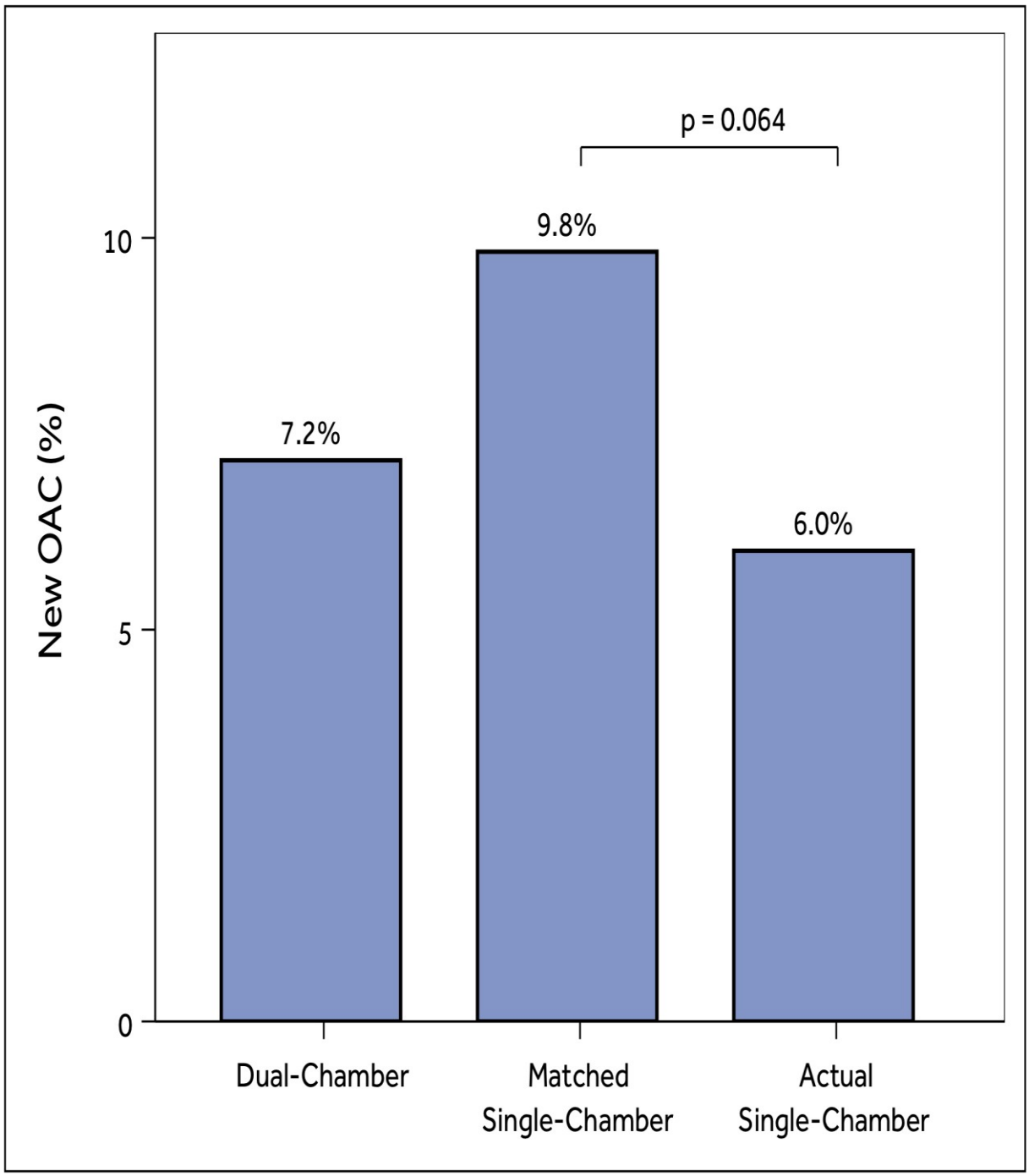


Figure 3. Incidence of New Oral Anticoagulation. The bars represent incidence of new oral anticoagulation (OAC) initiation in the first 24 months, estimated with the Kaplan-Meier method. Actual and matched single-chamber groups are compared with a log-rank test.



TABLES

Table 1. Baseline Characteristics for all 1,862 CRT, Dual-Chamber and Single-Chamber Subjects

Patient characteristics at baseline	**CRT-D (N = 639)**	**Dual-chamber (N = 649)**	**Single-chamber (N = 574)**	**P-value***
Demographics and Clinical Presentation				
Male (N, %)	468 (73.2%)	519 (80.0%)	456 (79.4%)	0.83
Age (years)	66.5 ± 11.3	61.9 ± 13.0	60.0 ± 12.1	0.007
LVEF (%)	27.9 ± 9.5	35.0 ± 14.9	33.6 ± 13.7	0.092
QRS duration (msec)	152.5 ± 27.1	113.3 ± 27.1	105.4 ± 20.6	< 0.0001
Secondary prevention (N, %)	108 (16.9%)	245 (37.8%)	185 (32.2%)	0.048
NYHA class (N, %)				0.27
I	31 (4.9%)	131 (20.2%)	157 (27.4%)	
II	198 (31.0%)	285 (43.9%)	259 (45.1%)	
III	368 (57.6%)	94 (14.5%)	74 (12.9%)	

Patient characteristics at baseline	**CRT-D (N = 639)**	**Dual-chamber (N = 649)**	**Single-chamber (N = 574)**	**P-value***
IV	15 (2.3%)	3 (0.5%)	4 (0.7%)	
No Heart Failure	27 (4.2%)	136 (21.0%)	79 (13.8%)	
History (N, %)				
Coronary artery disease**	382 (59.8%)	419 (64.6%)	376 (65.5%)	0.76
Myocardial infarction	217 (34.0%)	255 (39.3%)	260 (45.3%)	0.037
Congestive heart failure	313 (49.0%)	181 (27.9%)	177 (30.8%)	0.28
Hypertension	344 (53.8%)	339 (52.2%)	252 (43.9%)	0.004
Previous device, any	241 (37.7%)	176 (27.1%)	114 (19.9%)	0.003
Conduction Defects (N, %)				
Sinus Node Dysfunction	40 (6.3%)	55 (8.5%)	14 (2.4%)	<0.0001
AV block	116 (18.2%)	93 (14.3%)	37 (6.4%)	< 0.0001
Left bundle branch block	381 (59.6%)	63 (9.7%)	35 (6.1%)	0.021
Right bundle branch block	48 (7.5%)	46 (7.1%)	31 (5.4%)	0.24
Medication use (N, %)				

Patient characteristics at baseline	**CRT-D (N = 639)**	**Dual-chamber (N = 649)**	**Single-chamber (N = 574)**	**P-value***
ACE inhibitor / ARB	531 (83.1%)	471 (72.6%)	432 (75.3%)	0.30
Aldosterone Antagonist	274 (42.9%)	178 (27.4%)	162 (28.2%)	0.80
Beta-Blocker	550 (86.1%)	544 (83.8%)	487 (84.8%)	0.64
Diuretic	520 (81.4%)	358 (55.2%)	306 (53.3%)	0.53
Anti-Arrhythmic	79 (12.4%)	108 (16.6%)	61 (10.6%)	0.003
Anticoagulant	95 (14.9%)	99 (15.3%)	81 (14.1%)	0.63
Antiplatelet	416 (65.1%)	441 (68.0%)	401 (69.9%)	0.50

LVEF, Left Ventricular Ejection Fraction; NYHA, New York Heart Association; AV, Atrioventricular; ACE, Angiotensin Converting Enzyme; ARB, Angiotensin II Receptor Blocker.

* p-values are for comparison between single-chamber and dual-chamber ICDs. Tests used are Student t-test, Fisher exact test, and Cochran-Mantel-Haenszel test for NYHA class.

** Coronary artery disease as reported is derived from checkboxes for ischemic cardiomyopathy, coronary artery disease, prior myocardial infarction, coronary artery bypass graft, and coronary artery intervention.

Table 2: Incidence of AT/AF endpoints at 24 months estimated using the Kaplan-Meier method. Endpoints are based on AT/AF burden thresholds, and AT/AF-related complications in patients who had a first episode of AT/AF.

AT/AF duration	CRT-D	Dual-Chamber	Matched Single-Chamber*
≥ 6 minutes	29.7% (25.7% - 33.5%)	26.6% (22.8% - 30.2%)	22.0% (18.3% - 25.5%)
≥ 6 hours	16.3% (13.0% - 19.4%)	13.1% (10.1% - 15.9%)	9.8% (7.1% - 12.4%)
≥ 24 hours	9.9% (7.3% - 12.4%)	7.1% (4.9% - 9.3%)	6.3% (4.1% - 8.5%)
≥ 7 days	8.2% (5.8% - 10.6%)	3.8% (2.1% - 5.5%)	3.4% (1.8% - 5.0%)
AT/AF related complication**	37.7% (26.2% - 47.4%)	34.9% (21.1% - 46.3%)	33.5% (19.7% - 44.9%)

AF, Atrial Fibrillation; AT, Atrial Tachycardia

* Single-Chamber was estimated by propensity score weighting of Dual-Chamber patients

** Any serious adverse event with evidence of atrial fibrillation, thrombosis, stroke or transient ischemic attack which occurs after the first AT/AF episode